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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,717	05/08/2002	Audrey Goddard	P3230R1C001-168	8617

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KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER	
WEGERT, SANDRA L	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 04/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,717	GODDARD ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11-14 and 16-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-14 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

In view of the papers filed 28 October 2004, the inventorship in this nonprovisional application has been changed by the deletion of: Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen and Colin K. Watanabe.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

The Amendment, submitted 28 October 2004 has been entered. Claims 9, 10 and 15 are canceled.

Claims 1-8, 11-14 and 16-20 are under examination in the Instant Application.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior Office action.

Withdrawn Objections And/or Rejections

URL's.

The objection to the Specification because it contained browser-executable code, is *withdrawn.* Applicants amended the Specification to remove all URL's (28 October 2004).

Continuity

The objection to the Specification for not complying with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119, is *withdrawn,* based on Applicant's arguments (page 10, 28 October 2004). The filing date of the Provisional Application (16 September 1998) is considered as the priority date.

35 U.S.C. § 112, first paragraph-, Written Description.

The rejection of Claims 1-8, 11-14 and 16-20 under 35 U.S.C. § 112, first paragraph, Written Description, is *withdrawn in part.* Applicants amended claims to insert language pertaining to functional regions of SEQ ID NO: 92 that had not been identified (i.e, "extracellular domains"), but have not removed references to amino acids having 80-99% sequence identity to the claimed PRO1327 polynucleotide or disclosed polypeptide (see below).

35 USC § 112, First Paragraph - Deposit Rules

The rejection of Claims 1-8, 11-14 and 16-20 under 35 U.S.C. § 112, first paragraph, for not complying with the enablement requirement, is *withdrawn in part.* Specifically, Applicants amended the Specification to insert language guaranteeing unrestricted availability of the deposited nucleic acid molecules (clone DNA66521-1583), and pointed out that the instant Specification lists the ATCC address. Please see sections on 35 USC §101 and §112, 1st paragraph (below) for maintained portions of the rejection.

35 USC § 102(b)

The rejection of Claims 16 under 35 U.S.C. 102(b,) for being unpatentable over Ohara, et al, (1999, Accession No. AB032985), is *withdrawn* based on Applicant's arguments that the effective filing date of the instant Application is 16 September 1998 (page 10, 28 October 2004).

Maintained Objections and/or Rejections

35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.

Claims 1-8, 11-14 and 16-20 are rejected under 35 U.S.C. 101, as lacking utility.. The reasons for this rejection under *35 U.S.C. § 101* are set forth at pp. 3-9 of the previous Office Action (29 July 2004). Claims 1-8, 11-14 and 16-20 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office Action (29 July 2004), one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue (28 October 2004, pages 10-13) that the results presented in the instant Specification are enabling for the antibody that binds the polypeptide of SEQ ID NO: 92. They argue that the PRO1327 polypeptide is a diagnostic marker for normal esophagus, one esophageal tumor, normal stomach and a stomach tumor sample, and point to the results of the amplification assay which showed an approximately 2-fold amplification of the PRO1327 DNA in these two tissues.

Applicant's arguments (28 October 2004) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the Specification provides data showing a very small increase in DNA copy number- about 2 fold- in several samples of cancer tissue and several normal tissues. However, there is no evidence regarding whether or not PRO1327 mRNA or polypeptide levels are also increased in these tissues. Furthermore, as discussed in the previous Office Action (29 July 2004, pages 5 and 6), what is often seen is a *lack* of correlation between DNA amplification and increased peptide levels (Pennica, et al, 1998, Proc. Natl. Acad. Sci., 95: 14717-14722). As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to the results presented, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2: 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Similarly, Chen et al. (2002, Molecular and Cellular Proteomics 1: 304-313) disclose that twenty-eight of the 165 protein blots (17%) or 21 of 98 genes (21.4%) had a statistically

significant correlation between protein and mRNA expression (see Abstract and Table I). In addition, their results showed that no significant correlation between mRNA and protein expression was found (r= -0.025), if the average levels of mRNA or protein among all samples were applied across the 165 protein blots (98 genes). The reference also teaches that the mRNA/protein correlation coefficient varied among proteins with multiple isoforms, indicating potentially separate isoform-specific mechanisms for the regulation of protein abundance. In this study using a quantitative analysis of mRNA and protein expression within the same lung adenocarcinomas, it is showed that only a minority subset of the proteins exhibited a significant positive correlation with mRNA abundance.

Given the small increase in DNA copy number of PRO1327, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels. Further research needs to be done to determine whether the small increase in PRO1327 DNA supports a role for the antibody in detecting or treating cancerous tissue; such a role has not been suggested by the instant disclosure. The requirement for further research makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,

> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the Specification's assertions that the claimed PRO1327 antibodies have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

The Declaration of Dr. Ashkenazi, filed under 37 CFR 1.132 (28 October 2004), is insufficient to overcome the rejection of claims 1-8, 11-14 and 16-20, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action (29 July 2004).

Likewise, the Declaration of Dr. Polakis, filed under 37 CFR 1.132 (28 October 2004), is insufficient to overcome the rejection of claims 1-8, 11-14 and 16-20, based upon, 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action.

The Declaration of Dr. Grimaldi, filed under 37 CFR 1.132 (28 October 2004), is insufficient to overcome the rejection of claims 1-8, 11-14 and 16-20, based upon 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph as set forth in the last Office action (29 July 2004).

In the Declaration filed under 37 CFR 1.132 (28 October 2004), staff scientist Ashkenazi claims that the purpose of the experiments that measured increases in gene copy number was to identify tumor cell markers useful for cancer treatment (page 1, Declaration, 28 October 2004) and to identify cancers for which there was an absence of gene product over-expression (page 2). The Ashkenazi declaration argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has

been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, as discussed above, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial.

Dr. Grimaldi (declaration filed under 37 CFR § 1.132, 28 October 2004) states that the gene amplification assay was used to differentiate tumor [tissue] from normal (see paragraph 6), and that the levels of gene expression are irrelevant: "what matters is that there is a relative difference in expression between normal tissue and tumor tissue" (paragraph 7). These points have been fully considered but are not found to be persuasive. Firstly, it is important to note that the instant specification provides no information regarding increased protein, DNA or mRNA levels of PRO1327 in tumor samples as contrasted to normal tissue samples: Only gene amplification data were presented and then only in one normal tissue and one unrelated tumor tissue. The Declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1327 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1327 nucleic acid was amplified in some cancers and to a minor degree. No mutation or translocation of PRO1327 has been associated with lung tissue or melanoma. It is not known whether PRO1327 is expressed in cancerous lung or normal melanocytes or skin tissue, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that

the DNA encoding PRO1327 is amplified in a small number of samples, and invite the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Pennica et al. (1998, PNAS 95: 14717-14722), the issue is simply not predictable, and the specification presents a mere invitation to experiment.

As discussed above, and in the previous Office Action (page 5, 29 July 2004) this doubling of DNA levels in normal esophagus, one esophageal tumor, normal stomach and a stomach tumor sample is probably due to a doubling of chromosome number- an event that is very common in cancers. In addition, it has not been shown that RNA or protein levels are increased in these two tissues. For these reasons, the Declaration is insufficient to overcome the rejection of Claims 1-8, 11-14 and 16-20 based upon 35 U.S.C. § 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels.

Dr. Polakis (Declaration filed under 37 CFR § 1.132, 28 October 2004) states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in control tissues and that antibodies have been developed that identify and could possibly be used to downregulate the PRO peptides. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. He characterizes the instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is

not found to be persuasive. Firstly, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO1327 in tumor samples as contrasted to normal tissue samples: Only gene amplification data were presented. As discussed above, and in the previous Office Action (page 5, 29 July 2004) this doubling of DNA levels in cancer tissue is probably due to a doubling of chromosome number, an event that is very common in cancerous tissues. In addition, it has not been shown that RNA or protein levels are increased in these two cancers. For these reasons, the Declaration is insufficient to overcome the rejection of Claims 1-8, 11-14 and 16-20 based upon 35 U.S.C. § 101 and 112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Doctors Polakis, Grimaldi and Ashkenazi's' conclusions are provided in the declarations. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA Levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. See Hu et al. (2003, Journal of Proteome Research 2:405-412) as discussed above.

Applicants argue (page 9, 1st paragraph, 28 October 2004) that "if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level," and cite: Ørntoft, et al (2002, Mol. Cell. Proteomics, 1: 37-45). Ørntoft, et al do present data that indicates a correlation between increased gene copy number and increased protein expression (see Table 1, for example). However, their error rates varied from 31% to 50%.

Furthermore, since they knew the function of the genes for which they were staining, that error rate might be acceptable, if only that the expression assay can be combined with other functional assays, such that there would be a reason to detect those proteins. Such is not the case in the current Application. Applicants do not know the function of the PRO1327 polypeptide; indeed, the PRO1327 peptide has not been properly identified as yet. Therefore, it is not useful to detect a protein for which a function has not yet been identified, and additionally might only be overexpressed in one cancer, and for which error rates of detection may be as high as 30-50%.

Applicants argue (Response, 28 October 2004, pages 11 and 12) that even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of the evidence. Applicants provide evidence in the form of a publication by Hanna et al. (1999, Pathology Associates Medical Laboratories, 2 pages- attached to the Response of 28 October 2004). Applicants contend that the publication teaches that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over- expression of the HER-2/neu gene product. Applicant argues that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the instant rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the PRO1327 polypeptides and claimed antibodies is not in currently available form, the asserted utility is not substantial.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within ***TWO MONTHS of the mailing date of this final action and the advisory action is not*** mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire Later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
12 April 2005

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER